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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,169	01/02/2001	Cy A. Stein	55669-A-PCT-US/JPW/GJC	9695

7590 07/18/2005

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/753,169	STEIN ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-10-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's arguments with respect to the rejection of claims 5 and 43 under 35 USC 112, 1st paragraph, have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 3 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al. (WO 95/08350) in view of Goodchild (1990).

The instant claims are drawn to an antisense oligonucleotide comprising 10 or more contiguous bases of the nucleotide sequence set forth in any one of SEQ ID NOS: 1 and 3-13 wherein the oligonucleotide is conjugated to a peptide and wherein the oligonucleotide is complementary to a bcl-xL-encoding mRNA and inhibits translation thereof.

Reed discloses an antisense oligonucleotide comprising the following sequence: 3'.....ACAAAGGCATCCTGCAGTTG....5' (SA-AS; SEQ ID NO: 5 of Reed et al.) this sequence comprises a 7 base pair contiguous portion that is identical in sequence to nucleotides 7-13 of SEQ ID NO: 11 of the instant application. This antisense oligonucleotide comprises a sequence that is disclosed as being complementary to the Splice acceptor sequence of bcl-2 mRNA (specifically the underlined sequence) having the following nucleotide sequence:

5'...CCCC<u>CAACTGCAGGATGCCTTTGT</u>GGAACTACGG...3' (SEQ ID NO: 6 of Reed)

Reed et al. further teach that those skilled in the art to which the invention pertains, will appreciate that anticode oligomers having a greater or lesser number of substituent nucleotides, or that extend further along the bcl-2 mRNA in either the 3' or 5' direction than the preferred embodiments, but which also inhibit cell proliferation are also within the scope of the invention. (see page 13, Table 1, lines 1-18). Therefore, based upon the disclosure of Reed et al., at the time of the instant invention it would have been within the skill of the ordinary artisan to modify the SA-AS oligonucleotide by extending it in either the 5' or 3' direction along the bcl-2 mRNA. If the ordinary skilled artisan extended the 5' end of the SA-AS oligonucleotide, by adding more substituent nucleotides comprising a sequence that is complementary to the bcl-2 mRNA splice acceptor region disclosed in Table I, the following sequence would have been obvious to produce:

3'....AGTTCCACAAAGGCATCCTGCAGTTG....5' (SA-AS) with extended 5' end complementary to the following underlined sequences of the following *bcl-2* mRNA sequence as set forth in Table 1 : 5'...CCCCCAACTGCAGGATGCCTTTGTGGAACTACGG...3'(SEQ ID NO: 6 of Reed et al.). This obvious variation of the Reed et al. SA-AS oligonucleotide comprises a 10 base-pair contiguous portion that is complementary to SEQ ID NO: 11 of the instant application.

The disclosure of Reed et al. also teach that the oligonucleotides of their invention preferably include chemically modified derivatives, analogs, or comprise conjugates of the oligonucleotides and analogs thereof. Such conjugates, according to Reed et al. have properties to improve the uptake, pharmacokinetics, and nuclease resistance of the oligonucleotide, or the ability to enhance cross-linking or cleavage of the target sequence by the oligonucleotide (see

page 9, lines 19-29). Additionally, Reed et al. teach that the oligonucleotides of their invention may be combined with liposomes or other carrier means to protect the anticode oligonucleotides or analogues thereof from degradation until they read their targets and/or facilitate movement of the oligonucleotides across tissue barriers (see page 15, lines 1-6). Moreover, Reed et al. teach that it is expected that oligonucleotides presented to cells in the concentration range of about 0.001 μmolar to 100 μmolar will be effective to inhibit cell proliferation (see page 16, lines 1-8).

However, Reed et al. does not specifically teach wherein the disclosed antisense (anticode) oligonucleotide is conjugated to a peptide.

Goodchild (*Bioconjugate Chemistry, Vol. 1, No. 3, May/June 1990)* describes a variety of oligonucleotide conjugates, including for example polylysine (i.e. a peptide, see page 177, 1st col., paragraphs 5-6). See page 173, Table VI, for a list of groups known to be used as oligonucleotide conjugates, the list includes polypeptides. These oligonucleotide conjugates are designed to improve strength of hybridization and cellular uptake (see page 166, 1st col., 3rd paragraph).

It would have been obvious to the ordinary skilled artisan to have combined the teachings of Reed et al. and Goodchild et al. in the design of the instant invention, particularly antisense oligonucleotides comprising 10 or more contiguous bases of the nucleotide sequence set forth in SEQ ID NO: 11, comprising a peptide conjugate. One of ordinary skill in the art at the time of the instant invention, would have been motivated to design antisense oligonucleotides complementary to the portion of *bcl-2 mRNA* according to SEQ ID NO: 6 of Reed et al., since this portion of bcl-2 mRNA is disclosed by Reed et al. as being the splice acceptor site of bcl-2 mRNA, and a preferred region to design complementary oligonucleotides to be used anticode (or

antisense) oligonucleotides. An antisense oligonucleotide fully complementary to SEQ ID NO: 6 of Reed et al. would have the following sequence: *5'-AGTTCCACAAAGGCATCCT-GCAGTTGGGGG-3'*. The complementary antisense oligonucleotide would comprise 10 or more contiguous bases of the nucleotide sequence set forth in SEQ ID NO: 11 of the instantly claimed invention.

Moreover, one of ordinary skill in the art at the time of the instant invention would have been motivated to modify the anticode (antisense) oligonucleotides of Reed et al., which comprise 10 or more contiguous based of SEQ ID NO: 11, by conjugation with a peptide as per the teachings of Goodchild, since Reed et al. expressly states that the conjugates taught by Goodchild are purported to have properties to improve uptake, pharmacokinetics, and nuclease resistance of the oligonucleotide, or the ability to enhance cross-linking or cleavage of the target sequence by the oligonucleotide (see page 9, lines 19-29).

Therefore the invention as a whole would have been *prima facie obvious* over Reed et al. in view of Goodchild.

Double Patenting

4. Claims 5, 9, and 43 remain provisionally rejected under the judicially created doctrine of double patenting over claims 9, 36-50, 53-54, 58, and 61-62 of copending Application No. 09/832,648 in view of Manoharan et al. Sanghvi et al., Matteucci et al. and Arnold et al. for the reasons of record set forth in the prior Office Action mailed 6-18-03; and remain provisionally rejected over claims 37-43, 51-53, 58, and 61-62 of copending Application No. 10/160,344, for the reasons set forth in the Office Action mailed 5-19-04.

5. Applicant's arguments filed 5-12-05 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the claims of the co-pending applications referred to by the examiner have not been allowed (see page 3 of response, last paragraph). Contrary to Applicant's assertions, since the rejection over claims 5 and 43 has not been obviated by Applicant's amendments, the provisional double patenting rejections of the instant claims over Applications 09/832,648 and 10/160,344 are maintained. It is also noted that the instant application and copending applications 09/832,648 and 10/160,344, share at least one common inventor, and at least one common assignee.

6. The provisional double patenting rejection of claim 9 was improperly withdrawn in the Office Action mailed 2-05-2005. Although there is no other rejection of claim 9 other than the provisional double patenting rejection set forth above, as per MPEP § 804-I.B., the provisional double patenting rejection is maintained. MPEP § 804-I.B. states that "[T]he "provisional" double patenting rejection **should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application** unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications." In the

instant case, the provisional double patenting rejection is not the only remaining rejection in one of the conflicting applications.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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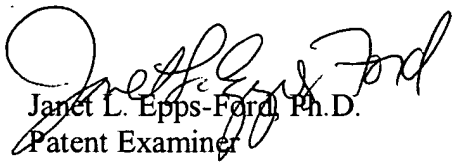

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1633

JLE